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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/997,542	11/15/2001	David Botstein	P2730P1C26	7269

35489 7590 02/28/2006

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ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 02/28/2006

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/997,542
Filing Date: November 15, 2001
Appellant(s): BOTSTEIN ET AL.

Daphne Reddy
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 1/26/06 appealing from the Office action mailed 8/11/05.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

09/989,726 and 09/993,604.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

WITHDRAWN REJECTIONS

The rejection of claims 119-121 and 123 under 35 USC 102 as being anticipated by Baker et al. has been withdrawn in view of the fact that the prior art document teaches no more than the instant invention.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Sen S. Curr. Opin. Oncol.. 12:82-88, 2000

Pennica D, et al. PNAS 95:14717-14722, 1998

Konopka JB et al. PNAS 83:4049-4052, 1986

Haynes PA, et al. Electrophoresis 19:1862-1871, 1998

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 101

A. Claims 119-121 and 123 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by a specific, substantial and credible asserted utility or a well-established utility. These claims are directed to antibodies to the polypeptide of SEQ ID NO:326. However, the invention encompassed by these claims has no apparent or disclosed patentable utility. This rejection is consistent with the current utility guidelines, published 1/5/01, 66 FR 1092. The instant application has provided a description of an isolated protein. However, the instant application does not disclose a specific and substantial biological role of this protein or its significance.

However, it is clear from the instant specification that the protein for the claimed antibody is what is termed an "orphan receptor" in the art. The instant application does not disclose the biological role of the protein or its significance. Appellants disclose in the specification that the receptor is a secreted protein. However, this fact, alone, is insufficient to confer utility to the protein of the present invention. Therefore, the instant claims are drawn to an antibody to a protein which has a yet undetermined function or biological significance. There is no actual and specific significance which can be attributed to said protein identified in the specification. For this reason, the instant invention is incomplete. In the absence of a knowledge of the natural ligands or biological significance of this protein, there is no immediately obvious patentable use for it. To employ a protein of the instant invention in the identification of substances which bind to and/or mediate activity of the said receptor is clearly to use it as the object of further research which has been determined by the courts to be a non-patentable utility. Since the instant specification does not disclose a "real-world" use for said protein then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 U.S.C. 101 as being useful.

Furthermore, since the protein of the invention is not supported by a specific and substantial asserted utility or a well-established utility, the antibody to the protein also lacks utility.

Claim Rejections - 35 USC § 112, first paragraph - enablement

A. Claims 119-121 and 123 are rejected under 35 U.S.C. 112, first paragraph, as failing to adequately teach how to use the instant invention. Specifically, since the claimed invention is not supported by a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 102

A. Claims 119-121 and 123 are rejected under 35 U.S.C. 102(a) as being anticipated by Tang et al. (WO 01/53312). The claims recite an antibody which binds to the protein of SEQ ID NO:326. The claims also recite a monoclonal, polyclonal, humanized, or labeled antibody. Tang et al. teach a protein which has numerous areas of 6 or more contiguous amino acids of SEQ ID NO:326 of the present invention (Sequence Comparison B). Tang also teach monoclonal, polyclonal, humanized and labeled antibodies as well as fragments thereof (pages 74-83).

Claim Rejections - 35 USC § 103

A. Claims 119-121 and 123 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weimann et al. (Genome Research) in view of Tang. The teachings of Tang are seen in the above rejection under 35 USC 102. Weimann et al. teach a protein which is 100% identical to approximately 522 contiguous amino acids of SEQ ID NO:326 of the present invention (Sequence Comparison C). Weimann do not specifically teach any of the antibodies claimed by the present invention. However, Tang do teach these antibodies. It would have been obvious for one of ordinary skill in the art at the time of the present invention to have made polyclonal, monoclonal, labeled or humanized antibodies in view of the teachings of Tang since the procedures for producing an antibody to the protein of Weimann is identical to those to produce the antibody of Tang. The artisan would have been motivated to make these antibodies in order to produce an antibody to isolate the protein (polyclonal), to a specific epitope of the protein of Weimann (monoclonal), or for detecting the protein (labeling) or any type of use involving humans, or the human variants of the protein of Weimann (humanized).

(10) Response to Argument

Claim Rejections - 35 USC § 101

Appellants begin their arguments by reciting numerous examples of case law. The Examiner takes no issue with the case law.

Appellants argue in the Brief that Example 170 of the specification discloses that the gene encoding PRO1281 showed significant amplification, ranging from 2.099 fold to 2.219-fold in different colon primary tumors. Therefore, such a gene is useful as a marker for the diagnosis of colon cancer, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy. Appellants also argue that the Declaration by Dr. Goddard supports the assertion that the gene is a suitable marker for the diagnosis of cancer.

These arguments have been considered, but are not deemed persuasive. First, it is pointed out that, respectfully, though Appellants state in the Brief that the results are "significant" there is no statistical analysis disclosed, nor is any formula disclosed showing how the data was analyzed in order to determine the significance of the amplification. Even if, as argued by Appellants with regard to the Goddard Declaration (see page 13 of the Brief), this 2-fold amplification was significant, again, this does not provide any significance to the encoded protein. However, it is noted that the Goddard Declaration states that:

> It is further my considered scientific opinion that an at least 2-fold increase in gene copy number in a tumor tissue sample relative to a normal i.e. non-tumor) sample is significant and useful in that the detected increase in gene copy number...

Therefore, it can be seen that this "significance" is based on opinion, not fact. In assessing the weight to be given expert testimony, the Examiner may properly consider, among other things, 1) the nature of the fact sought to be established, 2) the strength of any opposing evidence, 3) the interest of the expert in the outcome of the case, and 4) the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). Regarding the interest of the expert in the outcome of the case, it is noted that Dr. Goddard is employed by the assignee and is an inventor in this application. Furthermore, The Declaration of Dr. Goddard does not teach the level of reproducibility or the level of reliability of the results.

Appellants argue that the Sen et al. reference, as with the Goddard Declaration, supports Appellants' assertion that the gene of the invention possesses utility (re:aneuploidy and tumor markers). This argument has also been considered, but is not deemed persuasive. Appellants are attempting to provide utility to the protein of the invention (and, therefore, claimed antibody) based on information about the encoding DNA (gene). However, the fact that the gene may or may not have a utility does not necessarily confer a utility to the encoded protein, or to an antibody which binds said protein. This issue has been discussed throughout prosecution of this application regarding predicting protein levels based on DNA levels. The fact that Appellants used the well-known TAQMAN PCR assay does not persuade the Examiner since this assay is focused on DNA and does not relate to, nor provide any utility for any protein encoded by that amplified DNA, or the antibody to that protein.

Appellants argue that "it is not a legal requirement to establish a necessary correlation between an increase in the copy number of the DNA and protein expression levels that would correlate to the disease

state or that it is imperative to find evidence that DNA amplification is "necessarily" or "always" associated with overexpression of the gene product. Appellants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged." Based on this, Appellants argue that none of the references cited by the Examiner (Pennica et al , Konopka et al. and Haynes et al.) supports a lack of utility.

Applicants argue that Pennica do not teach any correlation to increased genes in general, only specifically for the WISP family. What can be gathered from Pennica, in the view of the Examiner, is that, based on the fact that one gene increased in cancer and one did not, that there is only a 50% chance of a gene increasing in a particular cancer. To further add to the unpredictability of gene overexpression in tumors, Applicants argue that Pennica teaches that this overexpression was seen in only 84% of tumors examined. Therefore, given the fact that there is only a 50% chance of finding a gene which may be overexpressed in tumors and that this gene is not even overexpressed on every occasion (84%), it seems difficult to predict that a gene will be overexpressed. In fact, in considering the information of Pennica, it seems more likely than not that a gene will *not* be overexpressed.

Applicants further argue that the Examiner's citing of Konopka was inappropriate since Konopka only teach the *abl* gene. This argument has been considered, but is not deemed persuasive. In fact, Konopka supports the Examiner's position that protein levels cannot be predicted from gene expression. This can be seen in Applicants' quotation from Konopka which states "Konopka et al. actually state that protein expression is not related to amplification of the abl gene but to variation in the level of bcr-abl m'RNA produced from a single Ph template." This, in view of Pennica, make a strong argument about predicting protein levels from DNA overexpression.

Furthermore, Haynes et al. contradict Applicants assertion that there exists a direct correlation between mRNA levels and the level of expression of the encoded protein. In fact, the literature cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissues. Although, Appellants argue that there is a well-established correlation in the art that the level of protein is positively correlated to the level of mRNA, as indicated above the polypeptide levels of Haynes et al. cannot be accurately predicted from mRNA levels. Therefore, there is no evidence to support Appellants' assertion that there is a working hypothesis among those skilled in the art is that there is a direct correlation between mRNA levels and protein levels. The Declarations and cited references do not establish a substantial utility for the claimed polypeptide. As stated above, the specification does not provide sufficient guidance to the skilled artisan to diagnose or treat any disease.

Though Haynes do not compare gene expression and protein levels, they do teach transcript levels and state that "correlation is 'not linear' and hence, 'one cannot accurately predict protein levels from mRNA [transcript] levels." Even if, as argued by Applicants, Haynes shows that it is more likely than not that mRNA levels correlate to protein levels, the present invention does not disclose mRNA levels, only DNA levels. Given the fact that Haynes is silent to DNA levels it can be assumed, especially in light of Pennica and Konopka, that DNA levels are not correlated (in general) to protein expression levels. Applicants argue that Omtoft, Pollack and Hyman show a general trend between protein and mRNA levels. Again, however, the present specification is concerned with DNA levels, not mRNA.

What can be concluded from Pennica, Konopka and Haynes as well as Appellants' citation of Hanna and Mornin is that there is not definite clear trend with regard to determining protein overexpression based on gene amplification data. Protein over-expression should be determined on a case-by-case basis.

Applicants further argue that the Examiner cited Hu et al. and referred to page 6 of the Office Action mailed 8/11/05. However, no reference to Hu could be found in that, or any other, Action.

Appellants further argue that Orntoft et al., Hyman et al., and Pollack et al. (made of record in Appellants' Response filed November 4, 2004) collectively teach that in general gene amplification increases mRNA expression. Appellants further argue that the Declaration of Dr. Paul Polakis (made of record in Appellants' Response filed November 4, 2004) shows that, in general, there is a correlation between mRNA levels and polypeptide levels and, therefore, supports these three references. Appellants further note that the sale of gene expression chips to measure mRNA levels is a highly successful business. Based on this, Appellants state that the central dogma is that the general rule is that protein levels can be predicted based on DNA/mRNA levels. Appellants submit that, "as evidenced by the Ashkenazi Declaration and the teachings of Hanna and Mornin (both made of record in Appellants' Response filed November 4, 2004), simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed." While it cannot be concluded that DNA and protein levels can, or cannot be correlated, what can be concluded, even given the Hanna and Mornin reference, is that the art is unclear as to whether or not protein levels can accurately be predicted from DNA levels. Therefore, given the body of evidence in the art showing "both sides of the story," even if Hanna and Mornin do teach the correlation of one DNA:protein exression relationship, or conclude that this is the general trend, no clear-cut results can be extrapolated to proteins in general, including the protein of the instant invention.

Regarding Orntoft et al., the reference appears to have looked at increased DNA content over large regions of chromosomes and comparing that to mRNA and polypeptide levels from the chromosomal region. Their approach to investigating gene copy number was termed CGH. Orntoft et al. do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. The instant specification reports data regarding cDNA amplification of individual gene, which may or may not be in a chromosomal region, which that is highly amplified. Orntoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (see page 40). This analysis was not done for the protein in the instant specification. That is, it is not clear whether or not PRO1281 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the relevance, if any of Orntoft et al. is not clear.

With regard to Polakis, only conclusions are provided in the Declaration and does not provide data such that the Examiner can independently draw conclusions. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Although, Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide, it is important to note that the instant specification provides no information regarding differential mRNA levels of PRO1281 in tumor samples as contrasted to normal tissue samples or the corresponding protein levels. Only mRNA expression data is presented. Therefore, the declaration is insufficient to overcome the rejection based upon 35 U.S.C. § 101 and 112, first paragraph, since it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels.

With regard to Appellants' argument that use of microarrays provides a utility for the present invention is not persuasive since, first, microarrays involve the use of DNA, not proteins. Second, it is the microarray as a whole which has been useful to the industry, not the individual genes.

It is believed that all pertinent arguments have been addressed.

Claim Rejections - 35 USC § 112, first paragraph - enablement

Claims 119-121 and 123 remain rejected under 35 USC 112, first paragraph, for the reasons already of record on page 5 of the Office Action dated 8/11/05 as well as for the reasons given in the above rejection under 35 USC 101. Applicants argue that the claimed invention is enabled because it has utility as argued previously. Applicants' arguments have been fully considered, but are not found to be persuasive for the reasons discussed above.

Claim Rejections - 35 USC § 102

Appellants submit that U.S. provisional application 60/141037 has utility based on the gene amplification assay and further that they have made a proper priority claim to U.S. provisional application 60/141037, filed June 23, 1999. Therefore, Tang et al. is not prior art. However, for the reasons presented above under 35 USC 101, Appellants' arguments are not deemed persuasive.

Claim Rejections - 35 USC § 103

Appellants submit that U.S. provisional application 60/141037 has utility based on the gene amplification assay and further that they have made a proper priority claim to U.S. provisional application 60/141037, filed June 23, 1999. Therefore, neither Weimann et al., nor Tang et al. is prior art. However, for the reasons presented above under 35 USC 101, Appellants' arguments are not deemed persuasive.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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